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Sulfoximine-substituted trifluoromethylpyrimidine analogs as inhibitors of proline-rich tyrosine kinase 2 (PYK2) show reduced hERG activity

Daniel P. Walker *, Michael P. Zawistoski, Molly A. McGlynn, Jian-Cheng Li, Daniel W. Kung, Peter C. Bonnette, Amy Baumann, Leonard Buckbinder, Janet A. Houser, Jason Boer, Anil Mistry, Seungil Han, Li Xing and Angel Guzman-Perez

Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, USA

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Dedicated to Professor Paul A. Grieco on the occasion of his 65th birthday

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ABSTRACT

The synthesis, in vitro properties, and in vivo pharmacokinetics for a series of sulfoximine-substituted trifluoromethylpyrimidines as inhibitors of proline-rich tyrosine kinase, a target for the possible treatment of osteoporosis, are described. These compounds were prepared as surrogates of the corresponding sulfone compound **1**. Sulfone **1** was an attractive PYK2 lead compound; however, subsequent studies determined this compound possessed high dofetilide binding, which is an early indicator of cardiovascular safety. Surprisingly, the corresponding sulfoximine analogs displayed significantly lower dofetilide binding, which, for *N*-methylsulfoximine (*S*)-**14a**, translated to lower activity in a patch clamp hERG K^+ ion channel screen. In addition, compound (*S*)-**14a** shows good oral exposure in a rat pharmacokinetic model.

Proline-rich tyrosine kinase 2 (PYK2) and focal adhesion kinase (FAK) are non-receptor tyrosine kinases, and together they constitute the FAK subfamily. Unlike FAK expression, which is ubiquitous, PYK2 expression is relatively restricted, with highest levels in the brain and hematopoietic system. Recent pharmacological and PYK2 knockout data demonstrate a link between inhibition of PYK2 and bone anabolism.[1] Hence, PYK2 represents a novel anabolic approach for treating osteoporosis. Currently FDA-approved oral agents to treat osteoporosis include bisphosphonates, estrogen, and selective estrogen receptor modulators (SERMs), all of which are antiresorptive in nature and are insufficient for restoring bone in critically osteoporotic patients. Parathyroid hormone 1–34 (Teriparatide)[2] is the only approved bone anabolic agent; however, it is an injectable that increases bone turnover with a balance favoring bone formation. Considering the usual challenges associated with protein-based therapeutics, such as inconvenient routes of administration, an orally bioavailable small-molecule PYK2 inhibitor represents an attractive anabolic therapy for patients afflicted by low bone mass and offers a new opportunity to impact this unmet medical need in the aging population.

Our prior work on PYK2 inhibitors focused on a trifluoromethylpyrimidine (TFMP) series.[3] Based on this work, PF-431396, a FAK selective inhibitor, was transformed into sulfone **1**, a potent PYK2 inhibitor with modest (17-fold) selectivity against FAK (Chart 1). Sulfone **1** was further attractive in that it was stable in human liver microsomes (HLM) and negative in a high-throughput reactive metabolite assay (RMA). However, subsequent studies on this compound found that it possessed significant activity in a dofetilide binding assay.[4] The dofetilide binding assay has been shown to be an effective screening tool for hERG blockade and

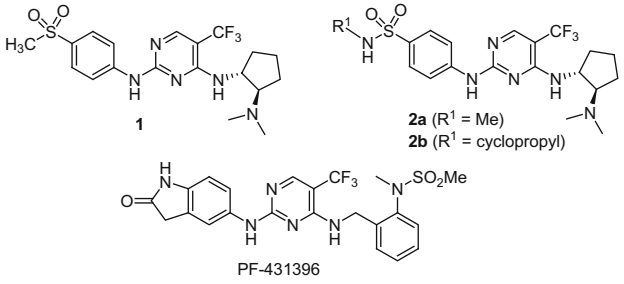

Chart 1. Selected PYK2 inhibitors.

* Corresponding author. Tel.: +1 636 247 1192.
E-mail address: daniel.p.walker@pfizer.com (D.P. Walker).

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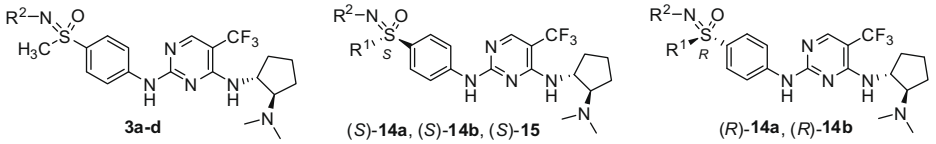
Table 1
Biological data for arylsulfoximine-substituted analogs



Compound	R^1	R^2	PYK2 IC_{50}[a] (nM)	PYK2 Cell IC_{50}[b] (nM)	FAK IC_{50}[c] (nM)	HLM Eh[d]	MDCK (A > B)[e] $P_{app} \times 10^{-6}$ cm/s	Dofetilide % binding[f]
PF-431396			31[1] (n = 12)	63 (n = 9)	1.0 (n = 12)	0.78	9.2	41
1			95 (n = 4)	60 (n = 4)	1300, 2000	<0.29	9.5	48
2a			140 (n = 4)	88 (n = 3)	3800 (n = 3)	0.66	5.3	50
2b			140, 260	95, 270	2100, 5800	0.74	4.8	76
3a		Me	67 (n = 4)	76, 110	1800, 2900	0.46	4.4	11
3b		Et	32 (n = 3)	10, 13	1100	0.54	4.7	5.9
3c		i-Pr_2	22 (n = 3)	34	ND	0.78	6.6	8.4
3d		H	65, 69	320 (n = 3)	ND	<0.29	1	12
(S)-**14a**	Me	Me	43 (n = 5)	29 (n = 3)	1100, 1700	0.45	5.1	1.1
(S)-**14b**	Me	Et	16 (n = 3)	22 (n = 3)	790	0.58	8.3	ND
(S)-**15**	Et	Me	21, 33	24, 46	ND	0.58	7.8	2
(R)-**14a**	Me	Me	67 (n = 3)	98 (n = 3)	2300	0.52	5.7	4
(R)-**14b**	Me	Et	63, 69	37, 67	2400	0.64	9.3	ND

[a] PYK2 fluorescence polarization (FP) protocol as described in Ref. 1. IC_{50} values represent the concentration to inhibit 50% of the phosphorylation of a peptide substrate relative to vehicle control. Numbers indicate IC_{50} values generated from individual 8-point concentration response relationships in triplicate.
[b] PYK2 LI-COR cellular assay as described in Ref. 19. Numbers indicate IC_{50} values generated from 9-point concentration response relationships in quadruplicate.
[c] FAK fluorescence polarization (FP) protocol as described in Ref. 1 using FAK kinase domain construct as described in Ref. 20. IC_{50} values represent the concentration to inhibit 50% of the phosphorylation of a peptide substrate relative to vehicle control. Numbers indicate IC_{50} values generated from individual 8-point concentration response relationships in triplicate.
[d] Eh = Hepatic extraction ratio, which is obtained from dividing estimated hepatic blood clearance of test compounds by the human hepatic blood flow of 20 mL/min/kg. Protocols for measuring half-lives in HLM and subsequent scaling to blood clearance have been published (see: Ref. 21).
[e] Madin Darby canine kidney cell permeability assay, apical to basel (A > B) permeability expressed as P_{app}.
[f] [^{3}H]-Dofetilide binding assay as described in Ref. 4. Numbers indicate the percentage inhibition of [^{3}H]-dofetilide binding to the hERG protein stably expressed on HEK-293 cells following a 10 μM dose of test compound.

proarrythmia.[5,6] With an increased awareness by the pharmaceutical industry and regulatory agencies on the liabilities associated with drug-induced QT prolongation, we felt it was important to minimize the hERG activity for compounds within this chemical series. We detail below our efforts to identify a novel compound with the same promising biological profile as sulfone **1** but with reduced hERG liability. This work led to the discovery of a novel series of arylsulfoximine-substituted TFMPs.[7]

During our search of possible surrogates for the sulfone moiety in **1**, we briefly considered sulfonamides. We prepared a 25 compound library of *N*-alkyl-, *N*-cycloalkyl- and *N*-heteroalkylsulfonamides. The best compounds to emerge from this library in terms of PYK2 enzyme and cellular activities were *N*-methyl sulfonamide **2a** and *N*-cyclopropylsulfonamide **2b** (Chart 1). These sulfonamides showed essentially equipotent PYK2 enzyme and cellular activities to that of sulfone **1** (Table 1). In fact, most of the compounds in the sulfonamide library showed equal PYK2 enzyme activity to that of sulfone **1**, although many displayed diminished PYK2 cellular activity (data not shown). The X-ray co-crystal structure of compound **2a** bound to PYK2 shows that the sulfonamide moiety of **2a** is partially solvent exposed (Fig. 1).[8] The binding mode of sulfonamide **2a** with PYK2 is quite similar to the binding mode of other related TFMPs, such as PF-431396 (Chart 1).[3,9] Given the structural similarities between compounds **1** and **2a**, it is likely that the sulfone moiety in **1** is also partially solvent exposed when bound to PYK2. Thus, it was not surprising that compounds **1** and **2a** have similar PYK2 enzyme activities. Unfortunately, neither sulfonamide **2a** nor **2b** showed any improvement in dofetilide binding, and both analogs were less stable in HLM compared to sulfone **1** (Table 1).

We next turned our attention to sulfoximines, which are monoimino analogs of sulfones. Sulfoximines are constitutionally and

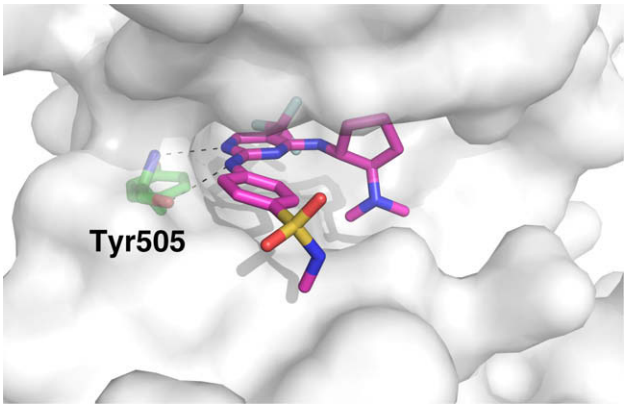


Figure 1. Crystal structure of compound **2a** (magenta) bound to PYK2. Dashed lines show hydrogen bond contacts to the hinge region.

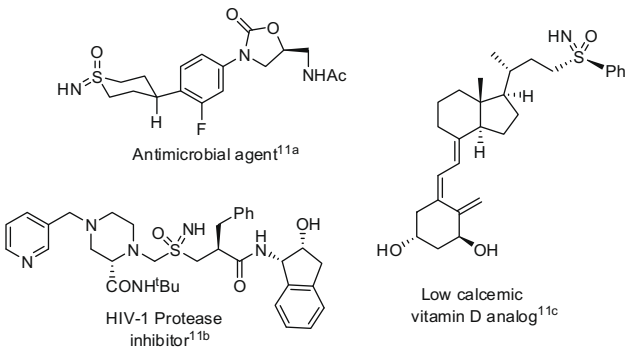
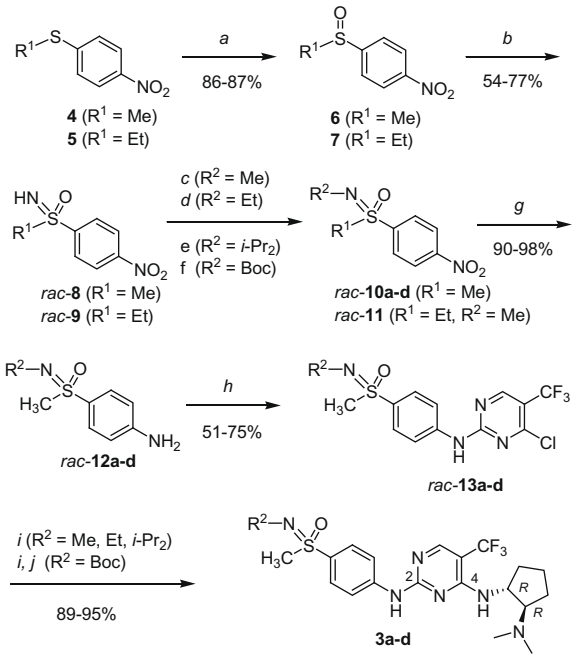


Chart 2. Biologically active substances possessing a sulfoximine.

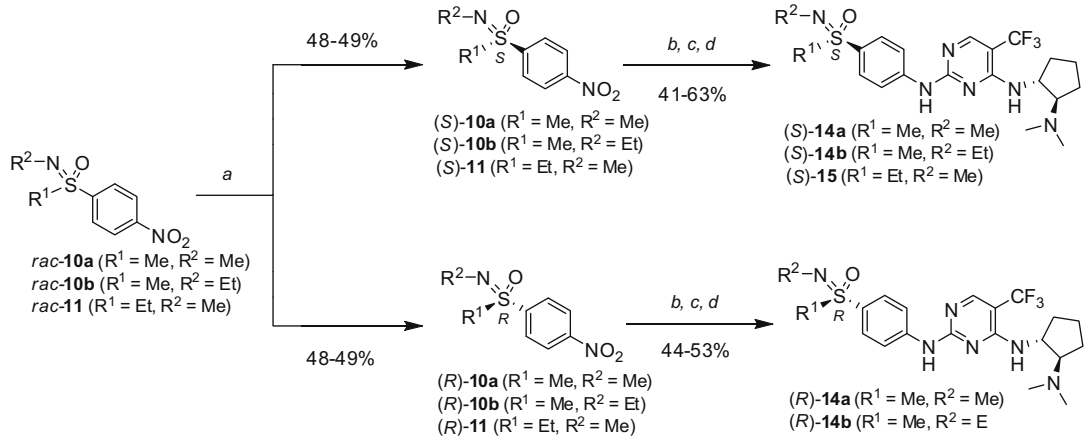


Scheme 1. General synthetic route for sulfoximine analogs. Reagents and conditions: (a) H_5IO_6 (1.05 equiv), $FeCl_3$ (0.03 equiv), CH_3CN, room temperature, 30 min; (b) NaN_3 (1.1 equiv), concd H_2SO_4, $CHCl_3$, 0 °C → 48 °C, 24 h; (c) 37% aq CH_2O, HCO_2H, 100 °C, 24 h, 95–98%; (d) NaH, DMF, 0 °C → room temperature, 30 min; EtI, 1 h, 78%; (e) NaH, DMF, 0 °C → room temperature, 30 min; 2-iodopropane, μW, 80 °C, 20 min, 24%; (f) $(Boc)_2O$, ^{t}BuOK, ^{t}BuOH, reflux, 48 h, 97%; (g) HCO_2NH_4 (excess), 20% $Pd(OH)_2$/C (cat.), MeOH, reflux, 2 h; (h) 2,4-dichloro-5-trifluoromethylpyrimidine, $ZnCl_2$ (1.0 M solution in Et_2O), 1,2-dichloroethane–^{t}BuOH (1:1), −5 °C, 1 h; add aniline **12**, −5 °C, 1 h; Et_3N −5 °C → 60 °C, 24 h; (i) (1*R*,2*R*)-*N*,*N*-dimethylcyclopentane–1,2-diamine, Na_2CO_3, DMF, 85 °C, 3 h; (j) HCl (4.0 M solution in dioxane), MeOH, room temperature, 4 h; $NaHCO_3$.

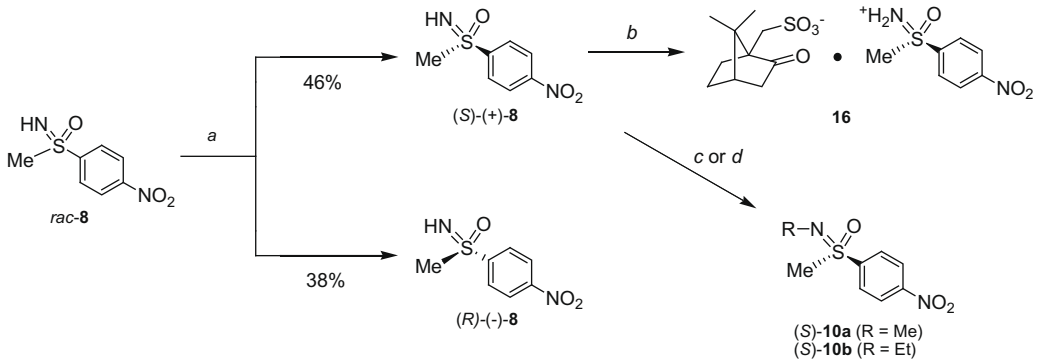
configurationally stable compounds that have gained considerable attention in synthetic organic chemistry.[10] Recently, a number of reports detailing the biological activities of sulfoximine-substituted analogs for the treatment of various diseases have appeared in the literature (Chart 2).[11]

The preparation of type **3** sulfoximines is described in Scheme 1. Thus, oxidation of sulfide **4** with periodic acid[12] gave the corresponding sulfoxide **6**. Under these conditions ca. 3–4% of the corresponding sulfone was formed. This was of little consequence as the sulfone impurity could be easily removed in the next step via an aqueous acid–base workup. Subjection of the sulfoxide to in situ generated hydrazoic acid afforded racemic sulfoximine *rac*-**8**.[13] Mono-methylation of the sulfoximine nitrogen in *rac*-**8** under Eschweiler–Clarke conditions gave rise (98%) to *N*-methylsulfoximine *rac*-**10a**.[14] *N*-Ethylsulfoximine *rac*-**10b** and *N*-*iso*-propylsulfoximine *rac*-**10c** were prepared via alkylation with the appropriate alkyl iodide.[15] Initial attempts to prepare *N*-Boc sulfoximine *rac*-**10d** using standard conditions [$(Boc)_2O$, Et_3N, MeOH] or [$(Boc)_2O$, aq NaOH, MeOH] failed to provide any of the desired product. However, the conditions of Bolm[16] employing ^{t}BuOK/^{t}BuOH together with di-*tert*-butyl dicarbonate proved quite effective. Transfer hydrogenation of the nitro group in *rac*-**10a–d** afforded the corresponding amines *rac*-**12a–d**. Regioselective addition of anilines *rac*-**12a–d** to the 2-position of 2,4-dichloro-5-trifluoromethylpyrimidine was accomplished via the use of $ZnCl_2$.[17] Treatment of chloropyrimidines *rac*-**13a–d** with enantiomerically pure (1*R*,2*R*)-*N*,*N*-dimethylcyclopentane-1,2-diamine gave rise (89–95%) to analogs **3a–d**, wherein each analog represents a 50/50 diastereomeric mixture of (*R*)- and (*S*)-sulfoximines.[18]

Biological data for sulfoximine analogs **3a–d** is detailed in Table 1. Sulfone **1** and PF-431396 are shown for comparative purposes. The sulfoximine analogs all showed similar PYK2 enzyme activity compared to the corresponding sulfone analog. Based on the similarities in structure for the sulfoximine analogs versus the sulfonamide analog and knowledge of the binding mode of sulfonamide **2a** to PYK2 (Fig. 1), it was not surprising that these compounds have very similar enzyme activities. The *N*-methyl and *N*-ethyl sulfoximine analogs show 30–35-fold selectivity against FAK, which is similar to the FAK selectivity shown for the sulfone and sulfonamide analogs. We were pleased to see that all the sulfoximines **3a–d** were active in a cell-based PYK2 assay, although sulfoximine **3d** showed a fivefold right shift in potency on going from the enzyme to the cell assay. The diminished cellular activity of **3d** is likely due to poor cell penetration and was consistent with the compound's weak performance in an MDCK cell permeability assay (Table 1). Sulfoximine analogs **3a**, **3b** and **3d** showed good to moderate stability in HLM, whereas *N*-*iso*propyl sulfoximine **3c** was unstable. Fortunately, all the sulfoximine analogs showed significantly lower dofetilide binding than either sulfone **1** or sulfonamides **2a,b**. The lower dofetilide binding for the sulfoximine analogs was unexpected given the subtle differences between these analogs and sulfone **1** or sulfonamides **2a,b**. Based on the overall biological activities shown by *N*-methylsulfoximine **3a** and *N*-ethylsulfoximine **3b**, these analogs were identified for further profiling.



Scheme 2. Preparation of diastereomerically pure sulfoximines. Reagents and conditions: (a) Chromatographic resolution [Chiralpak AS column, heptane–EtOH (70:30)]; (b) HCO_2NH_4 (excess), 20% $Pd(OH)_2$/C (cat.), MeOH, reflux, 2 h; (c) 2,4-dichloro-5-trifluoromethylpyrimidine, $ZnCl_2$ (1.0 M solution in Et_2O), 1,2-dichloroethane–^{t}BuOH (1:1), −5 °C, 1 h; add aniline, −5 °C, 1 h; Et_3N −5 °C → 60 °C, 24 h; (d) (1*R*,2*R*)-*N*,*N*-dimethylcyclopentane–1,2-diamine, Na_2CO_3, DMF, 85 °C, 3 h.



Scheme 3. Resolution of sulfoximine enantiomers. Reagents and conditions: (a) Chromatographic resolution [Chiralpak AS column, heptane–EtOH (70:30)]; (b) (−)-*R*-10-camphorsulfonic acid, MeOH, reflux, 10 min; (c) 37% aq CH_2O, HCO_2H, 100 °C, 24 h, 96%; (d) NaH, DMF, 0 °C → room temperature, 30 min; EtI, 1 h, 71%.

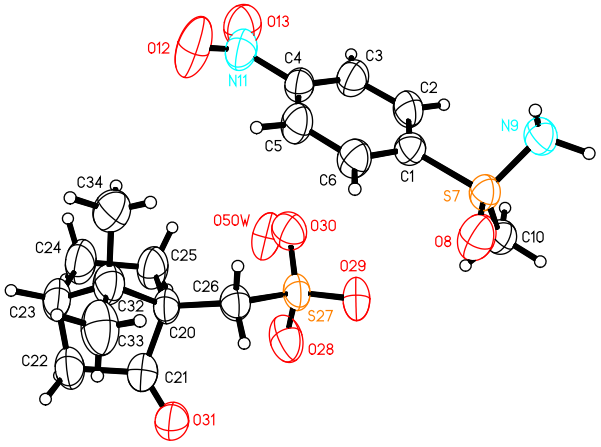


Figure 2. ORTEP diagram of compound **16**.

Prior to submitting sulfoximines **3a** and **3b** to additional biological assays, it was desired to prepare these analogs as diastereomerically pure compounds. Toward this end, chromatographic resolution of *N*-methyl sulfoximine *rac*-**10a** using a Chiralpak AS column afforded enantiomers (*S*)-**10a** and (*R*)-**10a** (Scheme 2). Diastereomerically pure sulfoximine analogs (*S*)-**14a** and (*R*)-**14a** were prepared in three steps from sulfoximines (*S*)-**10a** and (*R*)-**10a**, respectively. Diastereomerically pure *N*-ethylsulfoximines (*S*)-**14b** and (*R*)-**14b** were obtained in an identical manner to that described for the corresponding *N*-methylsulfoximines except *N*-ethylsulfoximine *rac*-**10b** was used as a starting material.

The absolute configuration of *N*-methylsulfoximine (*S*)-**10a** was unambiguously established as (*S*) by the sequence outlined in Scheme 3. Thus, chromatographic resolution of sulfoximine *rac*-**8** using a Chrialpak AS column gave rise to sulfoximine enantiomers (*S*)-(+)-**8**[23] and (*R*)-(−)-**8**. Salt formation of (*S*)-(+)-**8** with (−)-*R*-10-camphorsulfonic acid afforded a crystalline solid **16**. Single crystal X-ray analysis of sulfoximine **16** showed that it possessed the (*S*)-configuration (Fig. 2).[24] *N*-Methylation of (*S*)-(+)-**8** afforded sulfoximine (*S*)-**10a**, whose spectral properties were identical in all respects to (*S*)-**10a** prepared according to Scheme 2. Similarly, *N*-ethylation of sulfoximine (*S*)-(+)-**8** afforded sulfoximine (*S*)-**10b** (Scheme 3), which was identical in all respects to (*S*)-**10b** prepared according to Scheme 2.

The biological activity for individual diastereomers prepared in Scheme 2 is shown in Table 1. For the *N*-methylsulfoximine analogs, (*S*)-**14a** and (*R*)-**14a**, there was a modest preference for the *S*-sulfoximine diastereomer in the PYK2 cellular assay. Otherwise, no significant differences in activity were observed between the two *N*-methyl diastereomers for any of the assays in Table 1. Likewise, the same trend was observed for the corresponding *N*-ethylsulfoximines in that sulfoximine (*S*)-**14b** was slightly more potent against PYK2 than (*R*)-**14b**.

The final analog to be prepared in this study was *N*-methyl-*S*-ethylsulfoximine (*S*)-**15**.[25] This compound was prepared from ethyl 4-nitrophenyl sulfide[26] (**5**) by methods similar to those described for the other sulfoximine analogs (Schemes 1 and 2). Compound (*S*)-**15** displayed similar potency in the PYK2 enzyme and cellular assays to that of sulfoximines (*S*)-**14a** and (*S*)-**14b**. Sulfoximine (*S*)-**15** showed low dofetilide binding, which was consistent with the other sulfoximine analogs in the table. However, sulfoximine (*S*)-**15** showed decreased stability in HLM compared to the corresponding methyl sulfoximine analog (*S*)-**14a**. Based on the

Table 2
In vitro and in vivo data for selected compounds

Compound	RLM Eh[a]	RMA[b] (HML)	hERG IC_{50}[c] (μM)	rPPB[d] (*fu*)	Rat pharmacokinetic data[e]					
					CL (mL/min/kg)	MRT[f](h)	V_{dss} (L/kg)	C_{max} (μM)	AUC_{inf} (μM h)	C_{ave}[g] (μM)
1	<0.30	Negative	4.7	0.30	42	3.7	13	ND	ND	ND
(*S*)-**14a**	<0.30	Negative	20.3	0.36	74	2.3	13	0.72	5.0	0.21

[a] RLM, rat liver microsomes; in vitro compound stabilities (Eh) are reported as the fraction of compound remaining as compared to the concentration at t_0.
[b] RMA: Reactive metabolite assay as described in Ref. 27 using GSH–EE as a trapping agent in NADPH-supplemented HLM.
[c] hERG Patch clamp screen as described in Ref. 22. IC_{50} values represent the concentration to inhibit 50% of hERG current (IKr). Numbers represent IC_{50} values generated from 3-point concentration response relationships in duplicate.
[d] In vivo rat plasma protein binding, expressed as fraction unbound (f_u), determined at a drug concentration of 1 μg/mL.
[e] Clearance (CL), half-life and volume of distribution (V_{dss}) were generated following a 1.0 mg/kg iv dose in Sprague–Dawley rats. C_{max}, AUC_{inf} and C_{ave} were determined following a 10 mg/kg po dose in Sprague–Dawley rats. Numbers represent the means of two experiments.
[f] MRT: mean residence time.
[g] $C_{ave} = AUC_{inf}/t$, where t = dosing interval in h.

data in Table 1, sulfoximine (*S*)-**14a** was chosen for further profiling.

The bioactivation potential of sulfoximine (*S*)-**14a** was assessed in a high-throughput reactive metabolite assay (RMA) (Table 2). This screen examines the bioactivation of drug candidates in HLM via the detection of glutathione- (GSH) and/or glutathione ethyl ester- (GSH–EE) captured metabolites.[27] Bioactivation of drug candidates can lead to toxicological liabilities.[28] We were pleased to find that the sulfoximine analog (*S*)-**14a** was negative in this assay.

In vitro cardiovascular safety was assessed in a patch-clamp hERG K^+ channel screen (Table 2).[22] The hERG IC_{50} for compound (*S*)-**14a** was 20.3 μM; the corresponding sulfone analog (**1**) had an IC_{50} of 4.7 μM in the same assay. This represents a 4.3-fold improvement in the hERG activity for sulfoximine (*S*)-**14a**, which is significant considering the two compounds showed similar PYK2 cell potencies and similar plasma protein binding (Table 2). Given the similar log *D* values for (*S*)-**14a** and **1**,[29] the origin of reduced hERG activity for (*S*)-**14a** is not likely related to the lipophilicities of the two molecules. The reduction in hERG activity of (*S*)-**14a** could be attributed to the sulfoximine moeity disrupting the interaction of the adjacent phenyl ring within the hERG channel binding site.[30]

Plasma concentration–time profiles were obtained from rats receiving a parenteral dose (1 mg/kg, iv) of sulfoximine (*S*)-**14a**. The pharmacokinetic (PK) parameters of (*S*)-**14a** in rat best fit a non-compartmental model (Table 2). The clearance (CL) of (*S*)-**14a** (74 mL/min/kg) exceeded the hepatic blood flow in rat, which was significantly higher than that predicted by HLM or rat liver miscrosomes (Table 2). It is possible compound (*S*)-**14a** is undergoing non-cytochrome P450-mediated metabolism in vivo. This hypothesis is supported by the fact that the rat oral bioavailability of sulfoximine (*S*)-**14a** was 100%. Analog (*S*)-**14a** displayed a volume of distribution at steady state (V_{dss}) exceeding the total water volume in the rat (13 L/kg). The mean-residence time (MRT) of sulfoximine (*S*)-**14a** was roughly half that of the corresponding sulfone (**1**), indicating the sulfoximine compound was metabolically less stable than the corresponding sulfone. This is consistent with the HLM data, which also predicted that sulfoximine (*S*)-**14a** was metabolically less stable than sulfone **1**. However, despite the high in vivo CL of sulfoximine (*S*)-**14a**, the oral PK characteristics of this compound were sufficient to produce an average free plasma concentration (C_{avg}) of 76 nM following a single oral 10 mg/kg dose of the test compound. Thus, the average free plasma concentration of (*S*)-**14a** over 24 h exceeded the compound's PYK2 cell IC_{50} (29 nM) by 2.6-fold.

In summary, we have described the synthesis and SAR for a novel series of sulfoximine-substituted TFMPs. These compounds showed equal potency to sulfone **1** in the PYK2 enzyme assay and showed modest FAK selectivity. Except for compound **3d**, all sulfoximine analogs showed good PYK2 cellular activity and moderate stability in HLM. Unexpectedly, the sulfoximine analogs showed significantly less dofetilide binding than the corresponding sulfone or sulfonamide compounds. The improvement in dofetilide binding for sulfoximine **14a** translated to a 4.3-fold improvement in a hERG patch clamp K^+ channel assay. Furthermore, sulfoximine **14a** was found to have good oral exposure in a rat pharmacokinetic model. Future plans include profiling compound (*S*)-**14a** in additional safety-related assays as well as an animal efficacy model for osteoporosis.

Acknowledgments

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24. The data for compound **16** were collected on a Bruker APEX diffractometer at Pfizer Groton Laboratories, and all crystallographic calculations were facilitated by the SHELXTL system: $C_7H_9N_2O_3^+ \cdot C_{10}H_{15}S_1O_4^- \cdot H_2O$; Fw = 450.52; monoclinic; space group *P*2(1); unit cell dimensions: *a* = 8.703(3) Å, *b* = 6.959(2) Å, *c* = 17.243(6) Å with *b* = 93.099(10); volume = 1042.9(6) Å^3; Z = 2; D_{calcd} = 1.435 Mg/m^3; absorption coefficient = 2.735 mm^{-1}; *F*(0 0 0) = 476; GOF on *F*2 = 1.091; final *R* indices [$I > 2\sigma(I)$]: R_1 = 0.0428, wR_2 = 0.1093.
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30. See: Jamieson, C.; Moir, E. M.; Rankovic, Z.; Wishart, G. *J. Med. Chem.* **2006**, *49*, 1. and references cited therein.